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Statistical and Clinical Significance in ORBITA Placebo-Controlled PCI Trial

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We applaud ORBITA as a well-executed first placebo-controlled trial of the incremental impact of PCI on exercise time (ET) in stable angina.[1] However, given the study's importance, we were surprised by the statistics. Using an unpaired t-test, the authors compared change in ET between treatment groups and found "no difference" (16.6 seconds,95%CI:-8.9 to 42.0,p=0.20). However, in parallel randomized trials, mixed effects models such as an analysis of covariance (ANCOVA) are indicated as they carry more precision, correct for baseline imbalances that predispose to regression to the mean, and confer greater statistical power to detect small but clinically meaningful differences.[2,3] According to their exercise protocol,[4] a 16.6 second ET increment (on top of optimal drugs) brought PCI patients up into the ≥7.9 metabolic equivalent category linked to a 29% relative reduction in mortality.[5] Thus, the treatment effect might be clinically and statistically significant. At baseline, ET was unbalanced and higher in PCI patients (528.0±178.7 vs 490.0±195.0), implying that the treatment effect could be underestimated due to regression to the mean.[2,3] More importantly, an unpaired t-test shows that the end of study ET is statistically higher with PCI (556.3±178.7 vs 501.8±190.9,p=0.04) albeit without adjustment. Given that the baseline ET imbalance biases the results against PCI with change-over-time statistics, could the authors give us the ANCOVA p-value after adjustment for baseline ET. Because hesitant use of PCI could conceivably harm patients, it is imperative that the ORBITA results remain publically valid even after more appropriate ANCOVA testing.

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